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LETTERS TO THE EDITOR

Asymmetric Synthesis of a Phosphorus Analog of Natural γ-amino-β-hydroxybutyric Acid

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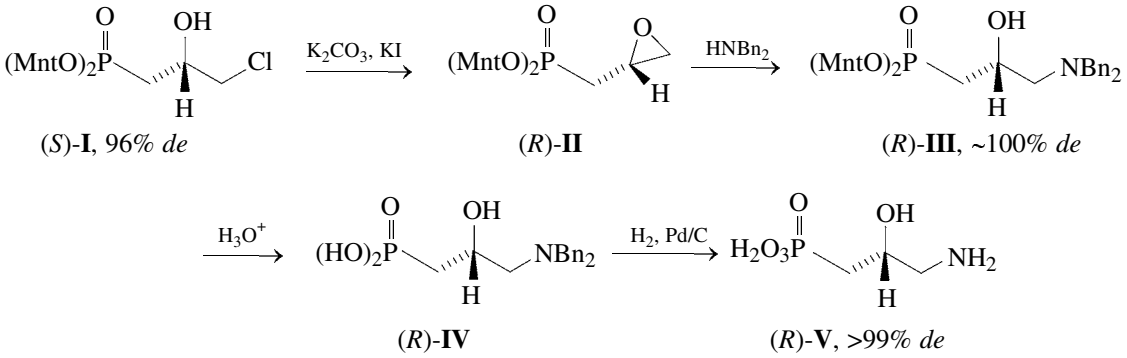
We have developed a simple synthesis of a phosphorus analog of natural γ-amino-β-hydroxybutyric acid (GABOB) which is important in the biological aspect and used for treatment of some deseases of nervous system [1, 2].

In the first step, the pure (*S*)-dimenthyl 3-chloro-2-hydroxypropylphosphonate (**I**) we prepared earlier [3, 4] was dehydrochlorinated with potassium carbonate in acetonitrile in the presence of potassium iodide to form epoxide (*R*)-**II** with a high stereospecifity and without loss of optical purity.



Compound **II** was reacted with dibenzylamine to obtain crystalline hydroxyaminophosphonate (*R*)-**III**. The latter was further dealkylated by heating with hydrochloric acid in dioxane to afford crystalline phosphonic acid (*R*)-**IV** which was debenzylated by hydrogenation in methanol with palladium on charcoal. As a result, a crystalline phosphorus analog of natural γ-amino-β-hydroxybutyric acid (*R*)-**V** was prepared with good yield and high optical purity. The structure of compound (*R*)-**V** was confirmed by elemental analysis and NMR spectroscopy. The enantiomeric purity of diastereomeric compounds **I**–**III** was monitored by NMR spectroscopy. The *R* configuration of compound **V** was established by measuring its optical rotation [5, 6]. Due to the presence of menthyl groups, compounds **I**–**III** could be isolated and purified by crystallization, i.e. we could exclude chromatographic purification from the synthetic procedure and prepare an optically pure phosphorus analog (*R*)-**V**.

Bis[(1*R*,2*S*,5*R*)-menthyl] (2*R*)-(oxiran-2-yl)-methylphosphonate (II). To a solution of 1.156 g of compound **I** [4] in 19 ml of acetonitrile–DMF (10 : 3.5) we added 0.707 g of potassium carbonate and a catalytic amount of potassium iodide. The mixture was refluxed for 8 h, the precipitate was then filtered off, and the solvent removed to obtain compound **II** as a yellowish oil, yield 98%, $[\alpha]_D^{20}$ –62.4° (*c* 7.0, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm

(*J*, Hz): 0.8 d (3H, *J* 7); 0.88 d (3H, *J* 7); 0.89 d (3H, *J* 7); 0.90 d (3H, *J* 7); 0.91 d (3H, *J* 7); 0.8–1.65 m (16H, CH_2C); 2.15–2.05 m (2H, PCH_2); 2.4 d.d (1H, *J* 2.1, *J* 5.1); 3.0 d.d (1H, *J* 4, *J* 4.8); 3.0 m (1H, C*H*OH); 4.24 m (2H, CHO*H*). ^{31}P NMR spectrum ($CDCl_3$): δ_P 25.3 ppm.

Bis[(1*R*,2*S*,5*R*)-menthyl] (2*R*)-[3-(dibenzylamino)-2-hydroxypropyl]phosphonate (III). To a solution of 1.1 g of compound **II** in 20 ml of methanol we added 0.52 g of dibenzylamine. The mixture was refluxed for 20 h. The solvent was removed, and the residue was recrystallized from acetonitrile. The product is a colorless crystalline compound, yield 70%, mp 73°C, $[\alpha]_D^{20}$ –45.92 (*c* 4.57, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm (*J*, Hz): δ, ppm (*J*, Hz): 0.73 d (3H, J_{HH} 7.2, CH_3); 0.80 d (3H, J_{HH} 6.9, CH_3); 0.87 d (3H, J_{HH} 7.0, CH_3); 0.90 d (3H, J_{HH} 7.0, CH_3); 0.91 d (3H, J_{HH} 7.0, CH_3); 0.92 d (3H, J_{HH} 7.0, CH_3); 2.0 d.d.d (J_{HP} 12.5, J_{HH} 1.2, PCH^a); 2.13 d.d.d (*J* 14.1, *J* 7.8, *J* 2.7, PCH^b), 1.2–2.2 m (16H, CH_2C); 4.1 m (2H, CHO), 3.55 c (4H, CH_2Ph). 1.829 d.d.d (*J* 33.9, *J* 18.6, J 3.6, CH_2N), 7.1–7.3 m (10H, C_6H_5). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 30.0. Found, %: C 72.64; H 9.51; P 5.08. $C_{37}H_{58}\cdot NO_4P$. Calculated, %: C 72.63; H 9.55; P 5.06.

(2*R*)-[3-(Dibenzylamino)-2-hydroxypropyl]phosphonic acid hydrochloride (IV). To 0.75 g of compound **III** in 30 ml of dioxane we added 10 ml of conc. HCl, and the mixture was kept for 3 days at 80–85°C. The mixture was evaporated, and the residue was dissolved in 15 ml of water and washed with benzene. After removal of water in a vacuum, the product was obtained as a colorless hygroscopic crystalline compound, yield 85%. ^1H NMR spectrum (CDOD), δ, ppm (*J*, Hz): 1.73 d.d.d (J_{HP} 32.4, J_{HH} 17.4, J_{HH} 8.1, CH^aP), 1.93 d.d.d (J_{HP} 34.5, J_{HH} 14.7, J_{HH} 4.5 CH^bP), 3.00 d.d (J_{HH} 13.2, J_{HH} 9.3, CH^bN), 4.08–4.21 m [1H, CH(OH)], 4.95 s (3H, OH); 7.52–7.54 m (10H, C_6H_5). ^{31}P NMR spectrum (H_2O): δ_P 26.5 ppm.

(2*R*)-(3-amino-2-hydroxypropyl)phosphonic acid (V). To a solution of 0.39 g of compound **IV** in 45 ml of ethanol we added 0.37 g of palladium on charcoal (10%). Gaseous hydrogen was passed through a stirred mixture for 20 h. Then the mixture was filtered, the filtrate was evaporated, and the product was washed with acetone and dried in a vacuum. A colorless hygroscopic compound was obtained, $[\alpha]_D^{20}$ +8.3° (*c* 1.2, H_2O), ^{31}P NMR spectrum: δ_P 22.8 ppm. The product was additionally purified on KU-2 cationite, yield 90%, $[\alpha]_D^{20}$ +10.2° (c_1, H_2O). ^1H NMR spectrum (D_2O), δ, ppm (*J,* Hz): 1.78 d.d.d (J_{HH} 31.2, J_{HH} 15.0, J_{HH} 6.3, CH^aP), 1.86 d.d.d (J_{HH} 32.1, J_{HH} 14.7, J_{HH} 6.3, CH^bP), 2.99 d.d (J_{HH} 13.5, J_{HH} 8.5, CH^aN), 3.27 d.d (J_{HH} 13.1, J_{HH} 3.4, CH^bN), 4.14 m [1H, CH(OH)]. ^{31}P NMR spectrum (D_2O): δ_P 18.1 ppm. Found N, %: 9.43. Calculated N, %: 9.03.

The NMR spectra were measured on a Varian-300 instrument against internal TMS (^1H) and external 85% H_3PO_4 in D_2O (^{31}P). The optical rotations were measured on a Polax-2L polarimeter (Japan).

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